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# Convenient Synthesis of 1-Alkoxy-1,2-dihydrophosphinine 1-Oxides by Ring Enlargement

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## ABSTRACT

*The addition of dichlorocarbene to the double bond of 1-alkoxy-dihydrophosphole oxides and subsequent thermolysis of the adduct so obtained affords mixtures of the two double bond isomers of alkoxy-dihydrophosphinine oxides, if the latter step is carried out in the presence of triethylamine. Experimental data support the involvement of a cationic intermediate during the opening of the cyclopropane ring. A simplified procedure for the preparation of the starting dihydrophospholes is also presented.*

## *INTRODUCTION*

1,2-Dihydrophosphinine oxides can be the starting materials for the synthesis of phosphorus heterocycles [1–3] such as the seven-membered phosphepine oxides [1] or the bridged heterocyclic compounds [2, 3]. The latter products, which are obtained in Diels–Alder reactions, are used as precursors to generate low-coordinated fragments [2–5].

One approach to the synthesis of dihydrophosphinine oxides involves the ring enlargement of 2,5-dihydro-1H-phosphole 1-oxides [2, 6, 7]. By the method of Quin et al. [2, 6] 3-methylphosphole derivatives can be converted to dihydrophosphinines in four steps. According to this procedure the ozonolysis of the phosphole to a dicarbonyl compound is followed by intramolecular aldol condensation, reduction, and dehydration steps. Alkyl- or aryl-substituted dihydrophosphinine oxides are also obtained through the adducts of dihydrophosphole oxides with dichlorocarbene by thermolysis. This method, reported recently by us [7], is not suitable for the preparation of the alkoxy-dihydrophosphinines; direct thermolysis of the alkoxy-substituted adducts is expected to give phosphinic acids instead of the esters, as demonstrated in the thermolysis of the methoxy-substituted adduct **2a** [7]. To avoid this problem, an indirect route through the hydroxy-tetrahydrophosphinine oxide by dehydration has been suggested for the preparation of the methoxy-dihydrophosphinine oxide **3a** [1, 8] (Scheme 1). In this paper we show that the alkoxy-dihydrophosphinine oxides can be obtained directly from the adducts, if the thermolysis is carried out in the presence of triethylamine. This method offers a simple, two-step route to alkoxy-dihydrophosphinine oxides from dihydrophosphole oxides.

## *RESULTS AND DISCUSSION*

The starting materials, 1-alkoxy-dihydrophosphole oxides (**1a–d**), were prepared by the alcoholysis of the isoprene and phosphorus tribromide cycloadduct. The original procedure of Hunger et al. [9], however, was modified at two points: the alcohol served also as solvent, and sodium carbonate was used in solid form instead of aqueous solution. Dihydrophosphole oxides (**1a–d**) described earlier in the literature have also been characterized by IR and mass spectroscopic methods.

The first key step, the cyclopropanation of the alkoxy-dihydrophosphole oxides (**1a–d**), was carried out under phase-transfer catalytic conditions in a liquid–liquid two-phase system using 50% aqueous sodium hydroxide and chloroform (Ma-

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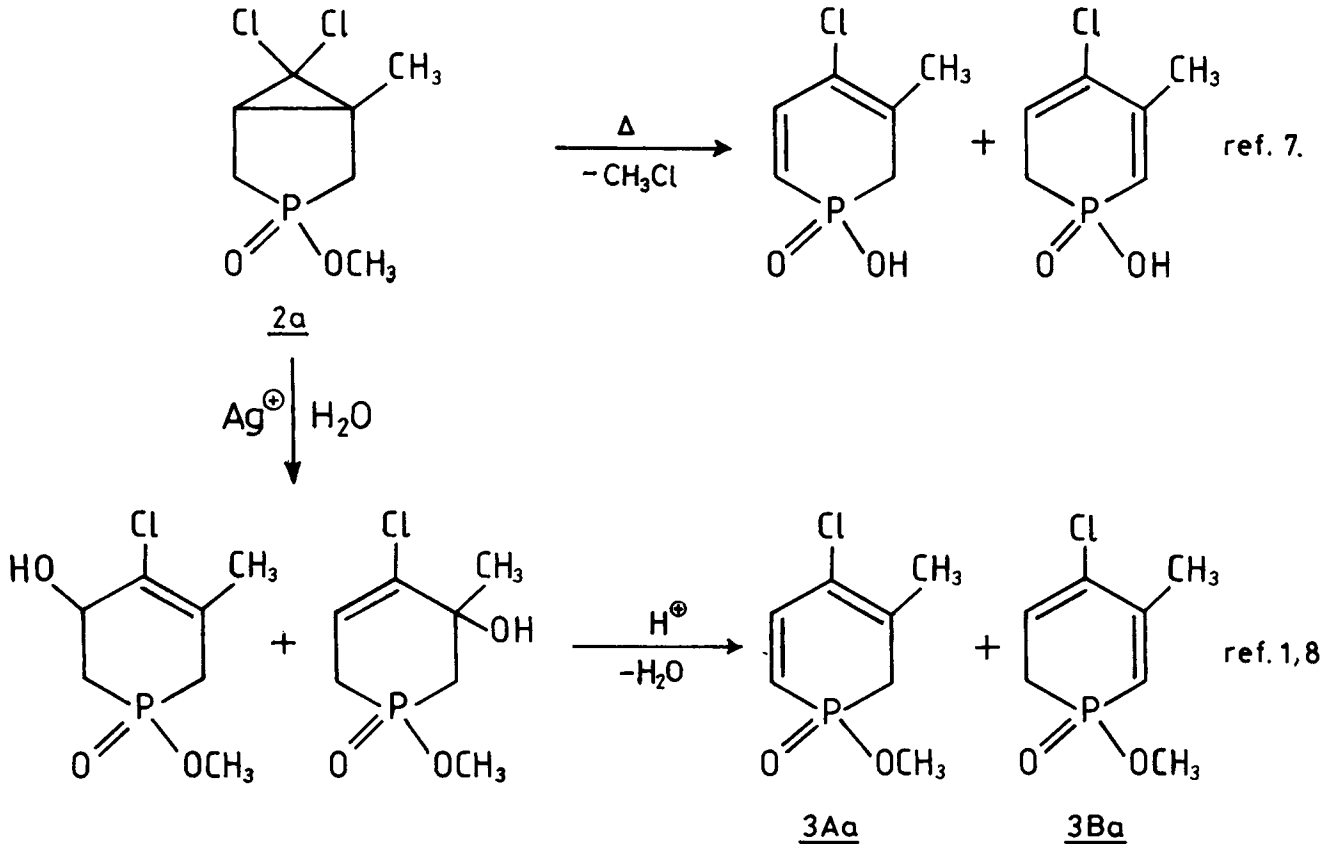
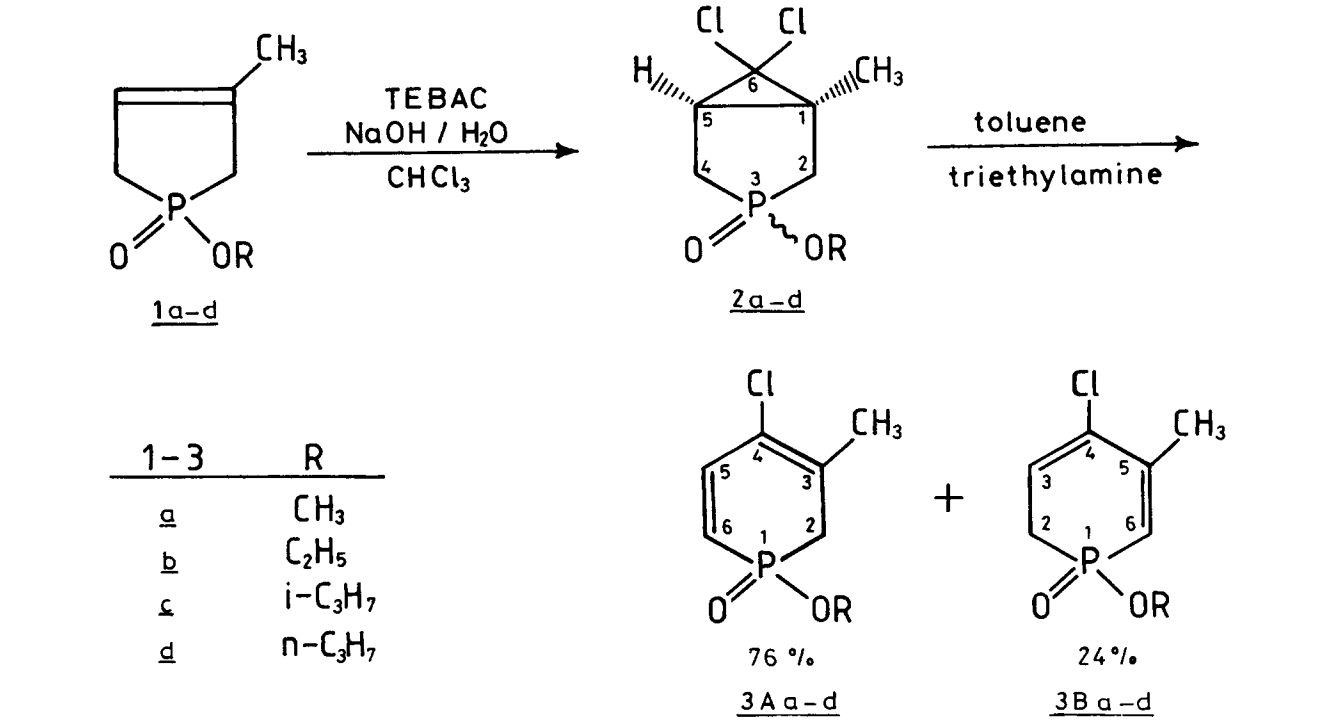



**SCHEME 1**




| 1-3 | R |
|---|---|
| a | $CH_3$ |
| b | $C_2H_5$ |
| c | $i\text{-}C_3H_7$ |
| d | $n\text{-}C_3H_7$ |

**SCHEME 2**

**TABLE 1** $^{13}C$ NMR Data for the Regioisomers **A** and **B** of Dihydrophosphinine Oxides **3b–d** in $CDCl_3$ Solutions

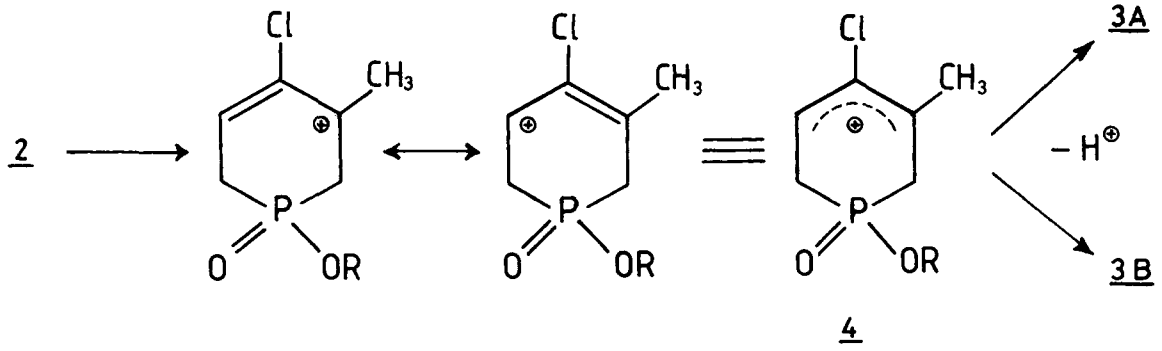
| | $\delta\ ^{13}C$ ($J_{PC}$ in Hz) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Product*[a] | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | C—$CH_3$ | R $C_\alpha$ | $C_\beta$ | $C_\gamma$ |
| **3Ab** | 33.2 | 122.9 | 131.7 | 144.3 | 118.7 | 22.9 | | | |
| | (99.0) | (21.3) | (8.8) | — | (120.2) | (10.3) | 60.2 | 16.2 | |
| **3Bb** | 27.6 | 123.2 | [b] | 150.3 | 118.0 | 24.3 | (6.6) | (5.1) | |
| | (98.2) | (10.3) | | — | (126.0) | (14.6) | | | |
| **3Ac** | 33.7 | 122.6 | 131.6 | 143.7 | 119.5 | 22.8 | 69.2 | 23.7 | |
| | (99.6) | (22.0) | (8.8) | — | (120.9) | (10.3) | (5.9) | (3.7) | |
| **3Bc** | 28.1 | 123.2 | 130.5 | 149.6 | 118.7 | 24.2 | 68.9 | 23.9 | |
| | (98.9) | (10.3) | (22.7) | — | (126.0) | (13.9) | (5.1) | (3.7) | |
| **3Ad** | 32.9 | 122.7 | 131.6 | 144.1 | 118.6 | 22.8 | | | |
| | (99.7) | (22.0) | (8.1) | — | (120.9) | (11.0) | 65.5 | 23.4 | 9.4 |
| **3Bd** | 27.3 | 123.1 | 131.1 | 150.1 | 117.8 | 24.2 | (6.6) | (6.6) | — |
| | (98.2) | (10.3) | (22.0) | — | (126.0) | (14.7) | | | |

[a]For numbering, see structures **3A** and **3B**.
[b]Not resolved.

kosza method [10]). Because the alkoxy substitution promotes the addition of the electrophilic carbene [11] to the double bond, the cyclopropanation takes place relatively easily, and the adducts (**2a–d**) can be obtained in reasonable yields after flash column chromatography (59–71%) (Scheme 2). Two chemical shifts were found in the $^{31}P$ NMR spectra of the products **2a–d** showing that two diastereoisomers are formed under the conditions used. The relative intensity of the $^{31}P$ NMR signals revealed a ratio close to 1 : 1 for products **2b–d**. Elemental analysis, mass, and IR spectroscopic data confirmed the gross structure of the adducts. Adducts **2b–d** are new compounds, whereas one of the diastereoisomers of product **2a** was described earlier [12].

As observed in the thermolysis of the alkyl- or aryl-substituted dihydrophosphole–dichlorocarbene adducts [7], the cyclopropane ring of the alkoxy-substituted adducts (**2a–d**) also suffers opening on heating. These reactions, however, give phosphinic acids instead of the esters, as the fission of the alkoxy group by the hydrogen chloride liberated during the cyclopropane ring opening also occurs. According to our experience the course of the thermolysis can be changed if the hydrogen chloride formed is removed from the mixture with one equivalent of triethylamine. In this way alkoxydihydrophosphinine oxides (**3a–d**) are the sole products of the reaction. Thermolysis, carried out at the optimum temperature in boiling toluene, gives the products **3a–d** primarily in good yields after column chromatography. Similarly to the reaction of the P–C-substituted adducts [7], mixtures containing the two regioisomers (**A** and **B**) of the alkoxy-dihydrophosphinines (**3a–d**) are produced from adducts **2a–d** on heating (Scheme 2). The presence of the two regioisomers (**A** and **B**) was supported by the two chemical shifts in the $^{31}P$ NMR spectra of the products **2a–d** and by the two characteristic series of signals in their $^1H$ and $^{13}C$ NMR spectra. The NMR shifts and couplings, as well as the MS and IR data, are similar to the appropriate characteristics of the dihydrophosphinines described earlier [7, 8]. The $^{13}C$ NMR data of the new products **3b–d** are listed in Table 1, and $^{31}P$ and $^1H$ NMR data appear in Table 2.

The C-methyl groups of the regioisomers **A** and **B** can be well distinguished in the $^1H$ NMR spectra because the methyl group of the minor isomer **B** appears as a doublet ($J$ = 1.5 Hz) due to the allylic




**SCHEME 3**

**TABLE 2.** $^{31}P$ and $^{1}H$ NMR Data for the Regioisomers **A** and **B** of Dihydrophosphinine Oxides **3b–d** in $CDCl_3$ Solutions

| Product | Composition[a] (%) | $\delta\ ^{31}P$ | $\delta\ ^{1}H$ (*multiplicity* $J_{PH}$ in Hz) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | $R_1$ $H_\gamma$ | $R_1$ $H_\beta$ | 5-$CH_3$ | P-$CH_2$ | R $H_\alpha$ | olefinic H |
| **3b** | **A:** 76 | 32.3 | | 1.30 (t,7) | 1.98 (s) | 2.71 (d,18) | 4.06 (dq,7) | 5.80–7.10 |
| | **B:** 24 | 31.4 | | | 2.10 (d,1.5) | | | |
| **3c** | **A:** 76 | 30.0 | | 1.31 (d,7) | 2.02 (s) | 2.74 (d,19) | 4.67 (m) | 5.83–7.09 |
| | **B:** 24 | 29.2 | | 1.27 (d,7) | 2.11 (d,1.5) | 2.66 (d,19) | | |
| **3d** | **A:** 74 | 31.8 | 0.93 (t,7) | 1.69 (m) | 2.03 (s) | 2.76 (d,19) | 3.96 (dt,7) | 5.86–7.19 |
| | **B:** 26 | 30.9 | | | 2.13 (d,1.5) | 2.69 (d,19) | | |

[a]Determined from the relative intensity of the C—$CH_3$ signals.

coupling. The relative intensity of the C-methyl signals refers to the dominance of the **A** isomer (~76%) (Table 2).

Similar composition of the regioisomers **A** and **B** was established earlier, whether the dihydrophosphinines were obtained from the thermolysis of a single diastereoisomer of the P–C substituted adducts [7] or from the dehydration of the isomeric mixture of hydroxy-tetrahydrophosphinines [8]. The ratio for the regioisomers (**A** and **B**) in the product (**3a–d**) differs from that of the diastereoisomers of the starting adduct (**2a–d**). This can be explained assuming that the same intermediate is formed from both of the diastereoisomers. In accord with the mechanism suggested for the cyclopropane ring opening [7, 13], the involvement of a cationic intermediate (**4**) can be proposed (Scheme 3). Cation **4** is then stabilized with the loss of a proton to afford the regioisomers **A** and **B** of the product **3** in the characteristic ratio of ~76:24.

Finally, it should be noted that we have not been successful in separating the regioisomers **A** and **B** of the dihydrophosphinine 1-oxides **3a–d** by means of chromatography. The mixtures of the regioisomers can, however, be well utilized for certain purposes, for example, in the preparation of phosphepine oxides by ring enlargement, as the same product can be obtained from both of the regioisomers [1]. Other possibilities for the use of the regioisomeric mixtures are being examined.

## EXPERIMENTAL

The $^{31}P$ and $^{13}C$ NMR spectra were taken on a JEOL FX 100-MHz spectrometer operating at 40.26 and 25,0 MHz, respectively. $^{1}H$ NMR spectra were recorded on an Perkin–Elmer 60-MHz instrument. Chemical shifts downfield relative to 85% phosphoric acid and to tetramethylsilane, respectively, have a positive sign. All coupling constants are given in Hertz. Infrared spectra were recorded on a SPECORD 75 spectrometer. Mass spectra were obtained on a JEOL 01SG-2 instrument at 75 eV.

### *General Procedure for the Preparation of the Starting 1-Alkoxy-2,5-dihydro-3-methyl-1H-phosphole 1-Oxides* (**1a–d**)

To the appropriate alcohol (125 mL) in a dried, nitrogen-filled round-bottomed flask, 2,5-dihydro-3-methyl-1,1,1-tribromo-1H-phosphole [14] (67.7 g, 0.20 mol) is added with stirring and external ice-cooling over a 30-min period. Then the cooling bath is removed, and the contents of the flask is stirred further at room temperature for 2 h. Solid $Na_2CO_3$ (31.8 g, 0.30 mol) is then added to the mixture to neutralize the acid. The residue obtained after evaporating the solvent is taken up in chloroform (75 mL). The chloroform phases from the filtration and washing (20 mL) are combined, and the solvent is evaporated to give product **1a–d** after distillation. (Samples of **1** obtained with the omission of the final distillation are also suitable for further work.)

The following compounds were thus prepared:

*2,5-Dihydro-1-methoxy-3-methyl-1H-phosphole 1-Oxide* (**1a**) Yield 68%; bp 84–86°C/0.16 mb (lit [15] bp 124°C/13.3 mb); MS, m/z (relative intensity) 146 ($M^+$, 54), 68 (100); IR (neat) 1650, 1250, 1040 $cm^{-1}$.

*2,5-Dihydro-1-ethoxy-3-methyl-1H-phosphole 1-Oxide* (**1b**) Yield 64%; bp 85–88°C/0.13 mb (lit [9] bp 74–76°C/0.093 mb); MS, m/z (relative intensity) 160 ($M^+$, 33), 132 (13), 68 (100); IR (neat) 1645, 1250, 1045 $cm^{-1}$.

*2,5-Dihydro-3-methyl-1-*i*-propoxy-1H-phosphole 1-Oxide* (**1c**) Yield 60%; bp 86–89°C/0.13 mb (lit [16]: no bp is provided); MS, m/z (relative intensity) 174 ($M^+$, 15), 132 (21), 68 (100); IR (neat) 1650, 1245, 990 $cm^{-1}$.

*2,5-Dihydro-3-methyl-1-*n*-propoxy-1H-phosphole 1-Oxide* (**1d**) Yield 57%; bp 86–92°C/0.13 mb (lit [17] 123–124°C/10.7 mb; MS, m/z (relative intensity) 174 ($M^+$, 7), 132 (14), 68 (100); IR (neat) 1640, 1235, 1000 $cm^{-1}$.

### *General Procedure for the Preparation of 3-Alkoxy-6,6-dichloro-1-methyl-3-phosphabicyclo[3.1.0]hexane 3-Oxides* (**2a–d**)

A solution of sodium hydroxide (60.0 g, 1.50 mol) in water (72 mL) is added dropwise to a mixture of 1-alkoxy-2,5-dihydro-3-methyl-1H-phosphole 1-oxide (**1a–d**; 58.0 mmol), TEBAC (1.21 g, 5.32 mmol), and alcohol-free chloroform (180 mL) with stirring over a 1-h period. The temperature of the mixture gradually rises to reflux. After stirring for 5 h the mixture is filtered. A second portion of TEBAC (0.72 g, 3.16 mmol) is added to the organic phase made up to its original volume with chloroform. Then the mixture is reacted with another portion of sodium hydroxide (60.0 g, 1.50 mol) in water (60 mL) as above. The crude product obtained after drying ($Na_2SO_4$) and evaporating the solvent is chromatographed on silica gel, using chloroform (500 mL) and chloroform–methanol (99:1) as the eluants, to give the product **2a–d** as a mixture of two diastereoisomers.

The following products were thus prepared:

*6,6-Dichloro-3-ethoxy-1-methyl-3-phosphabicyclo[3.1.0]hexane 3-Oxide* (**2b**) Yield 71%; the ratio of the diastereoisomers is ~1:1; $^{31}P$ NMR ($CDCl_3$) $\delta$ +86.9 and +82.9; MS, m/z (relative intensity) 242 ($M^+$, 14), 214 (20), 207 (100), 179 (99), 79 (98), IR (neat) 1230, 1010, 870, 800 $cm^{-1}$. Anal. Calcd. for

$C_8H_{13}Cl_2O_2P$: C, 39.53; H, 5.39. Found: C, 39.32; H, 5.50.

*6,6-Dichloro-1-methyl-3-*i*-propoxy-3-phosphabicyclo[3.1.0]hexane 3-Oxide* (**2c**) Yield 66%; the ratio of the diastereoisomers is ~1:1 $^{31}$P NMR ($CDCl_3$) $\delta$ +85.4 and +80.9; MS, m/z (relative intensity) 256 ($M^+$, 3), 221 (44), 214 (74), 179 (100), 79 (90); IR (neat) 1250, 1000, 900, 830 $cm^{-1}$. Anal. Calcd. for $C_9H_{15}Cl_2O_2P$: C, 42.05; H, 5.88. Found: C, 42.30; H, 5.72.

*6,6-Dichloro-1-methyl-3-*n*-propoxy-3-phosphabicyclo[3.1.0]hexane 3-Oxide* (**2d**) Yield 59%; the ratio of the diasatereoisomers is ~1:1, $^{31}$P NMR ($CDCl_3$) $\delta$ +86.5 and +82.7; :MS, m/z (relative intensity) 256 ($M^+$, 3), 221 (22), 214 (21), 179 (85), 79 (100); IR (neat) 1250, 1005, 900, 830 $cm^{-1}$. Anal. Calcd. for $C_9H_{15}Cl_2O_2P$: C, 42.05; :H, 5.88. Found: C, 41.90; H, 5.95.

*6,6-Dichloro-3-methoxy-1-methyl-3-phosphabicyclo [3.1.0]hexane 3-Oxide* (**2a**) Yield 59%; the ratio of the diastereoisomers is ~2:1; $^{31}$P NMR ($CDCl_3$) $\delta$ +88.8 and +85.1 (only one isomer was found to form under milder conditions [12], $^{31}$P NMR ($CDCl_3$) $\delta$ +88.1); IR (neat) 1250, 1035, 895, 825 $cm^{-1}$.

### *General Procedure for the Preparation of 1-Alkoxy-4-chloro-1,2-dihydro-methylphosphinine 1-Oxides* (**3a–d**)

The mixture of the adduct (**2a–d**; 20.0 mmol) and triethylamine (2.78 mL, 20.0 mmol) in toluene (60 mL) is stirred at reflux for the appropriate time. Then water (10 mL) is added to the mixture, and after a short period of stirring the organic phase is separated and dried ($Na_2SO_4$). The solvent is evaporated, and the crude product is chromatographed on silica gel (2% methanol in chloroform) to give the product **3a–d** as a mixture of two regioisomers **A** and **B**.

The following compounds were thus prepared:

*3- and 5-Methyl-4-chloro-1,2-dihydro-1-ethoxyphosphinine 1-Oxide* (**3Ab** *and* **3Bb**) Reaction time 6 h; yield 60%; isomeric composition, $^{31}$P NMR and $^1$H NMR, Table 1; $^{13}$C NMR, Table 2; MS, m/z (relative intensity) 206 ($M^+$, 20), 178 (43), 114 (16), 79 (100); IR (neat) 1605, 1550, 1200, 1020 $cm^{-1}$. Anal. Calcd. for $C_8H_{12}ClO_2P$: C, 46.51; H, 5.85. Found: C, 46.21; H, 5.90.

*3- and 5-Methyl-4-chloro-1,2-dihydro-1-*i*-propoxyphosphinine 1-Oxide* (**3Ac** *and* **3Bc**) Reaction time 6 h; yield 76%; isomeric composition, $^{31}$P NMR and $^1$H NMR, Table 1; $^{13}$C NMR, Table 2; MS, m/z (relative intensity) 220 ($M^+$, 12), 178 (80), 114 (20), 79 (100); IR (neat) 1620, 1570, 1220, 990 $cm^{-1}$. Anal. Calcd. for $C_9H_{14}C10_2P$: C, 48.99; H, 6.40. Found: C, 49.13; H, 6.23.

*3- and 5-Methyl-4-chloro-1,2-dihydro-1-*n*-propoxyphosphinine 1-Oxide* (**3Ad** *and* **3Bd**) Reaction time 5 h; yield 65%; isomeric composition, $^{31}$P NMR and $^1$H NMR, Table 1; $^{13}$C NMR, Table 2; MS, m/z (relative intensity) 220 ($M^+$, 14), 178 (69), 114 (20), 79 (100); IR (neat) 1625, 1575, 1225, 1000 $cm^{-1}$. Anal. Calcd. for $C_9H_{14}C10_2P$: C, 48.99; H, 6.40 Found: C, 48.76; H, 6.28.

*3- and 5-Methyl-4-chloro-1,2-dihydro-1-methoxyphosphinine 1-Oxide* (**3Aa** *and* **3Ba**) Reaction time 6 h; yield 43%; the ratio of the regioisomers is 77:23; spectroscopic characteristics were similar to those reported earlier [1].

For analytical purposes samples of products **2** and **3** have been purified by repeated column chromatography.

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